PATENT COOPERATION TREATY

# PCT



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>SCB 797 PCT | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/EP 03/12699 | International filing date *(day/month/year)*<br>13.11.2003 | Priority date *(day/month/year)*<br>14.11.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K39/00 | | |
| Applicant<br>BRACCO IMAGING S.P.A. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 28.05.2004 | 05.01.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Greif, G<br>Telephone No. +49 89 2399-8659 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12699

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-23 as originally filed

**Claims, Numbers**

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,2,4-6,8-21 (all in parts)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,2,4-6,8-21 (all in parts) are so unclear that no meaningful opinion could be formed *(specify)*:

**see separate sheet**

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1,2,4-6,8-21 (all in parts)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 5-11,13-17,20,21 |
| | No: | Claims | 1-6,12,18,19 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-21 |
| Industrial applicability (IA) | Yes: | Claims | 1-21 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The following wording of claim 1 "tumours that in an individual patient expose on the cell surface only a number *n* smaller than *N* of *N* different altered forms that a given protein or glycoprotein of said tumour type can assume in a population of patients"
renders said claims unclear in the sense of Art. 6 PCT, since it would be an undue burden on the expert in the field to determine what types of tumours fall exactly under said definition.
Consequently, the definition of the recognition unit in part a. of claim 1 is also unclear, since it depends on *n*, *n* being unclear.
The same argument applies to claims 19, 20 and 21.

2. Claim 2 relates to a large number of possible compounds, namely immunoglobulins or fragments thereof, polypeptides and polysaccharides. The application however provides support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT only for a limited number of such compounds. Claim 2 therefore does not comply with Art. 6 PCT.

3. Claim 4 is not clear due to the term "fused genes with suitable linker regions". The application does not appear to give any example that would illustrate and support this kind of conjugation between recognition unit and diagnostic signal.

4. Claim 11 is not clear, since the term "wherein the unit able to provide a diagnostic signal or therapeutic effect is part of the bond between the recognition molecules of the recognition unit merely describes the goal to be achieved.

5. Claims 5 and 6 relate to a great number of possible proteins altered as a result of a variety of mutations, without defining them in any way, whereas the description gives support for a limited number of mutated proteins that are recognized by the claimed recognition molecules. Claims 5 and 6 do not fulfill the requirements of Art. 6 PCT.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Under Rule 66.1(e) PCT, a preliminary examination is not carried out on matter which has not been searched. Therefore, the preliminary examination has been carried out on the whole subject-matter of claims 3 and 7, and on the parts of claims 1, 2, 4-6 and 8-21 that have been searched.

2. Reference is made to the following documents:

   D1: WO 91/03493 A
   D2: EP-A-0 404 097
   D3: WO 93/11161 A
   D4: US-B-6 447 7761
   D5: ARTEAGA DE MURPHY C ET AL: "PHOSPHINE REDUCED IGG: A NEW METHOD FOR 99MTC LABELING IMMUNOGLOBULINS" JOURNAL OF RADIOANALYTICAL AND NUCLEAR CHEMISTRY, ARTICLES, ELSEVIER SEQUOIA S.A., LAUSANNE, CH, vol. 220, no. 1, 1997, pages 41-45,
   D6: EP-A-0 419 203
   D7: YASUSHI FUJIOKA ET AL: "Renal metabolism of 3'-iodohippuryl N-maleoyl - L-Lysine (HML)-conjugated Fab fragments" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 12, no. 2, March 2001 (2001-03), pages 178-185,
   D8: SAVIRANTA PETRI ET AL: "In vitro enzymatic biotinylation of recombinant Fab fragments through a peptide acceptor tail" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 9, no. 6, November 1998 (1998-11), pages 725-735

3. Novelty

   D1 discloses trimeric and tetrameric antibodies, including bispecific and trispecific F(ab)3 and F(ab)4 antibodies, which are linked via a o-phenylenedimaleimide linker. Said antibodies are used for targeting lymphoma cells. Said complex may also contain a pharmacological agent (the whole document). Claims 1-6, 12, 18, and 19 lack novelty over D1.

   D2 discloses antibodies against tumors, comprising oligospecific receptors which have oligovalent selectivity to the respective epitopes, whereby the antibodies can consist of immunoglobulins, and comprise a linker. Additionally, the compositions of D2 also refer to the use for treatment and diagnosis of target cells, in the form

of injection of a ligand which is cytotoxic and can be activated (p. 2, line 1 - p. 3, line 46; examples; claims 1-11). 1 March 20042 anticipates the subject-matter of claims 1, 2, 4-6, 12, 18, and 19.
D3 discloses multivalent antigen binding proteins, used as bispecific antigen-binding molecules, whereby the proteins comprise immunoglobulins such as Fab fragments, and where linkers link the polypeptides. The utilities comprise the guidance of a cytotoxic cell to a cancer cell that should be attacked (claims 1-18; p. 4, line 14 - p. 7, line 31; p. 13, line 8 -.p. 17, line 33). Claims 1-6, 12, 18 and 19 lack novelty over D3.

4. Inventive Step

4.1. D4 discloses monoclonal antibodies useful for the detection and therapy of gastric carcinoma, whereby the antibodies are directed against mutated E-cadherin protein, such as the loss of basepairs at exon 8, 9 or 10 (Table 2; column 4, line 66 - column 5, line 67; column 8, line 46 - column 9, line 58). Claims 7 and 8 are not considered to be inventive over the combination of D4 with D1, since the expert in the field gets a hint from D4 what mutations in cancers are useful targets, and would be prompted to prepare the compositions of D1 accordingly.

4.2. D5 and D6 disclose a technetium labelling method for immunoglobulins (the whole document), and the combination of D5 or D6 and D1 renders claims 11, 12, 14, 17, and 18 non-inventive)

4.2. D7 discloses radiolabeled antibody fragments for targeted therapy, where radioactive iodine is used to label Fab-fragments (the whole document). Claims 12 and 13 lack inventive step over D1 in combination with D6.

4.3. D8 discloses the biotin-avidin linking system in the production of targeted compositions comprising Fab fragments. Thus, claims 9, 10, 20 and 21 are not inventive over D8 in combination with D1.

4.4. Claims 15 and 16 are not considered to contain inventive subject-matter, since they disclose mere alternatives to diagnostic signals, that are well known in the art and do not contribute to the solution of the problem.